Journal of Cardiovascular Disease Research

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

FORMULATION & IN-VITRO EVALUATION OF FLOATING MICRO BALLOONS OF RAMIPRIL

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ABSTRACT:

Floating drug delivery systems are planned for the less soluble, unbalanced and they have small bulk density than the gastric content similarly they float in the stomach for an extended period of time. From this the planning of floating microspheres is one of the method in conveying a dosage form to the target site in sustained controlled release manner, to reach respectable peak plasma concentration by growing bioavailability of drug or dosage form. In the floating microspheres, the drug overloaded microspheres arise in contact through gastric fluid the gel formers, poly saccharides and polymer hydrates to form a colloidal gel barrier then controls the rate of fluid diffusion into the device and consequential drug released by the inflated polymer depresses the density and float in the stomach. Associating to the conventional dosage form floating microspheres have enhanced G.I.T absorption, controlled release , site specificity and have probable to increase local action with extreme gastric retention time and expectable gastric emptying time. The aim of this work was to formulate and evaluate the floating microballoons containing Ramipril. The floating microballoons were prepared by solvent evaporation method with the polymer like of hydroxypropyl methyl cellulose and ethyl cellulose. The drug Ramipril was selected is an ACE inhibitor category and due to its short biological half-life and. poor bioavailability because of poor absorption at lower GI tract. In this research work my aim is to reduce the dosing frequency and single dose which release the active ingredient over an extended period of time.

Keywords: Floating Drug Delivery System, Solvent Evaporation Method, Ramipril, Buoyancy Test.

INTRODUCTION:

The oral drug delivery system display variable and small gastric emptying time, which result in imperfect drug release from the delivery system, leads to reduced effectiveness of administered dose. They are incapable to keep the drug concentration within curatively effective range for a required period. [1] To keep effective plasma drug concentration the incidence of dosing must be improved. To overawed these problem oral controlled drug delivery system are developed. Oral control drug delivery system having a problem for drugs whose absorption changes due to various factors such as dissolution, solubility, pH, enzymes and microbial floara. [2-4] Gastro retentive drug delivery system is one of the methods to rise the gastric retention time and localize the drug at the site of absorption. Gastro retentive drug delivery system are the system which are capable to prolong the retention time of the dose form in the gastric region and increase the bioavailability of the drugs that are mostly absorbed from upper GIT. [6-7] GRDDS extent the gastric residence time of drugs so that rise bioavailability, decrease drug waste, and increase solubility of drug. They prolong dosing interval, so that rise patient obedience. [8] For delivery of sparingly soluble and insoluble drugs gastro retentive dosage forms are very helpful. Methods being proposed to prolong the GRT include: Floating drug delivery system, swelling or expanding system, mucoadhesive system, modified shape system and other delayed gastric emptying devices. [9-10] FDDS is one of the methods for drugs having narrow absorption window in GI tract and give local action in upper part of small intestine. They are advantageous for treatment of peptic ulcer disease. [11]

FDDS are low density system. They have density lesser then gastric fluid, due to which they have affinity to float over the gastric content for prolong period of time without upsetting gastric emptying rate. As the system is floating on the gastric content, the drug is release gently at the desired rate from the system. [12-14] FDDS are appropriate for drugs having poor bioavailability because of narrow absorption window in the GIT.FDDS rise the bioavailability of drugs by holds the dosage form at the site of absorption. Ramipril is an angiotensin-converting enzyme (ACE) inhibitor, used to treat hypertension and congestive heart failure. [15-16] ACE inhibitors lower the production of angiotensin II, therefore relaxing arterial muscles while at the same time enlarging the arteries, allowing the heart to pump blood more easily, and increasing blood flow due to more blood being pumped into and through larger passageways. [17-18]

MATERIAL AND METHODS

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Materials:

Ramipril are purchased from Bangalore fine chem. All chemical and solvents used were of analytical grades and were used as obtained.

Methods:

Preformulation studies is the first step in the rational development of dosage form of a drug substance. It can be defined as an investigation of physiochemical properties of a new drug substance alone and with the excipients, to generate data useful to the formulator in developing safe, stable, potent, bioavailable and efficacious dosage form, which can be mass produced. [19] The goals of Preformulation studies are - To establish the physiochemical parameter of drug substance. To establish physical characteristics. [20] To establish compatibility with the common excipients. Hence, the following parameter were selected for the Preformulation studies for the pure drug. [21]

Melting Point Determination:

The melting point of Ramipril was determined by using melting point apparatus. The sample drug was taken in capillary tube which was closed by one sided and was placed in the melting point apparatus. The temperature was gradually increased automatically. The temperature at which sample was melted was noted. [22-23]

Solubility Studies:

The solubility of Ramipril was tested in various common solvents such as methanol, ethanol, ethyl acetate, butyl acetate and water. A semi quantitative determination of the solubility was made by adding solvent in small incremental amount to a test tube containing fixed quantity of solute. [24] After each addition, the system is vigorously shaken an examined visually for any undissolved solute particle. The solubility was observed only by the visual inspection. [25]

FTIR Spectral Studies:

The FT-IR studies of drug sample was taken and dried KBr were mixed by triturating. The mixture of sample and KBr was putted into the disk and pressed it to form pallet and placed the disk into sample holder insight the instrument. [26] Scanned it at the scanning range between 4000$^{cm\ -1}$ and 450 $^{cm\ -1}$. The spectra obtained were inter printed for the functional group. Any changes in parent pick of functional group as compare to pure drug pick will indicate drug polymer interaction. [27]

Determination of λ max for Ramipril:

Accurately weigh 100 mg of the pure Ramipril was transferred to 100 ml volumetric flask. The drug was then dissolved and diluted up to the mark with 0.1N HCL to get a concentration of 1000 µg/ml of stock solution. From the stock solution 10 ml was diluted with 100 ml of 0.1N HCL to get the concentration of 100 µg/ml solution. [28] From this solution aliquot of 0.2 ml was taken and diluted to 10 ml to get a concentration of 2 µg/ml and scanned over the wavelength of 200- 400 nm against 0.1N HCL as blank solution. The spectrum of absorbance versus wavelength was recorded using UV spectrophotometer and analysed for the absorption maximum the wavelength at which highest absorbance was observed. [29]

Determination of Calibration Curve:

From the above prepared solution (10 µg/ml), aliquots of 0.2, 0.4, 0.6, 0.8, 1.0 were pipette out and transferred to 10 ml volumetric flask and the volume was made up with the 0.1N HCL to get the concentration of 2, 4, 6, 8, 10 µg/ml respectively. [30] Absorbance of each of these solutions were recorded spectrophotometric ally at 225 nm.

Preparation of Floating Microballoons:

Microspheres containing Ramipril drug as a core material were prepared by an Emulsion Solvent Evaporation method. Drug, EC and HPMC were mixed in the mixture dichloromethane and ethanol at (1:1) ratio. The slurry was slowly introduced into 100 ml of liquid paraffin containing 10 Tween 80(1%) while being stirred at 500 rpm using mechanical stirrer equipped with three bladed propellers at room temperature. [31] The solution was stirred for 3.5 hour and allowed the solvent to evaporate completely and filtered by using filter paper. The microspheres obtained were washed repeatedly with petroleum ether until free from oil. The collected microspheres were dried at room temperature and subsequently stored in desiccators. Same procedure was repeated for all the batches. [32]

Table 1: Batch specification of Floating Microballoons

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Drug (mg)	100	100	100	100	100	100
Ethyl Cellulose (mg)	100	200	300	400	500	600
HPMC (mg)	100	100	100	100	100	100

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Ethanol (ml)	10	10	10	10	10	10
DCM (ml)	10	10	10	10	10	10
Tween 80 (ml)	1%	1%	1%	1%	1%	1%
Liquid Paraffin (ml)	90	90	90	90	90	90
Petroleum Ether (ml)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

HPMC: EC were used in the ratio of 1:1, 1:2, 1:3, 1:4, 1:5 and 1:6 respectively. Ethanol: DCM were used in the ratio of 1:1.

Evaluation of Floating Microballoons

Particle Size Determination

The particle size was determined by microscope.

Determination of entrapment efficiency (%):

50 mg of the microspheres were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCL repeatedly. The extract was transferred to a 100 mi of volumetric flask and the volume was made of using o.1N HCL. The solution was filtered and the absorbance was measured after suitable dilution spectrophotometric ally against suitable blank solution. After that entrapment efficiency was calculated according to the following relationship.

Entrapment efficiency % = Actual drug content

Theoretical drug content × 100

Test for Buoyancy:

Floating behaviour of hollow microspheres was studied in a 500 ml beaker by spreading the microspheres (100 mg) on a 0.1 N HCl containing 0.02% Tween 80 as a surfactant. After 10h, both the floating and the settled portions of microspheres were collected separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microsphere.

Buoyancy = Qf/Qs+Qf

Swelling Index:

A known weight of microspheres without drug was placed in 500 ml of different solution distilled water and enzyme free simulated gastric fluid (pH 1.2) and allow to swell for sufficient time at 500 ml beaker. The microspheres are removed, blotted with filter paper and their change in weight were measured during swelling until equilibrium was attained. Finally the weight of swollen microspheres was recorded after 4h and swelling ratio was calculated by the following formula –

$SI = (We - Wo) \times 100$

Where, We = weight of the swollen microspheres at equilibrium state

Wo = initial weight of dry microspheres

Determination of percentage yield:

The prepared microspheres were collected and weight. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres.

$$\% \text{ Yield} = \frac{\text{weight of microspheres}}{\text{Total weight of drug and polymer}} \times 100$$

***In vitro* drug release studies:**

The drug release studies were carried out using six basket dissolution apparatus USP type 1. The microspheres were place in a non-reacting mesh that had a smaller mesh size than the microspheres. The dissolution medium used was 900 ml of 0.1N HCL at 37.±2 ^{0}C. at a specific time interval, 1ml withdrawn and analysed by UV spectrophotometer at respective max. Value after suitable diluents against suitable blank. The withdrawn value was replaced with an equal volume of fresh 0.1N HCL.

Kinetic Treatment of Dissolution Data:

In order to describe the kinetics of the release process of drug in the different formulations, models were fitted to the dissolution data of optimized formulations using linear regression analysis. In order to study the exact mechanism of drug

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release from microsphere, drug release data was analysed according to Zero Order Kinetics, First Order Kinetics, Higuchi Model, Korsmeyer and Peppas Model. The criteria for selecting the most appropriate model was chosen on the basis of goodness of fit test.

Zero Order Kinetics:

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly assuming that area does not change and no equilibrium condition can be represented by the following equation:

$Q_t = Q_o + K_o (t)$

Where, Q_t is the amount of drug dissolve in time t.

Q_o is the initial amount of drug in the solution K is the zero order release constant.

First Order Kinetics:

The application of this model to drug dissolution studies used to describe absorption or elimination of drugs. To study the first order release rate kinetics the release rate data were fitted to the following equation.

$\text{Log } Q_t = \text{Log } Q_o + K_1 (t)/ 2.303$

Where, Q_t is the amount of drug released in time t.

Q_o is the initial amount of drug in the solution K_1 is the first order release constant.

Higuchi Model:

Higuchi describe drug release as a diffusion process based in the Fick's law, square root time dependent. Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semi – solid or solid mixture. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media, the equation is:

$Qt = KH. t 1/2$

Where, Q_t is the amount of drug released in time t and KH is higuchi dissolution constant.

Korsmeyer and Peppas Model:

This model is generally used to analyse the release of pharmaceutical polymeric dosage forms, when the release mechanism is not well known or when more than one type of release phenomena could be involved.

$M_t / M = K. t_n$

Where, M_t / M is the fraction of drug release K is the release constant and t is the release time, n is the diffusion exponent for the drug release that is dependent on the shape of the matrix dosage form.

RESULT AND DISCUSSION

Melting Point Determination:

The melting point of drug sample of Ramipril was found to be 111.3 ^oC (Table 7.1). After performing melting point test it was found that the melting point of Ramipril drug sample obtained in range (109-112 ^oC) as given in Indian Pharmacopoeia.

Table 2: Melting Point of Ramipril

S. No.	Melting Point (^oC)	Average (^oC)
1.	111	
2.	112	111.3
3.	111	

Solubility Studies:

Solubility of pure drug sample Ramipril was analysed with various solvents and found that Ramipril freely soluble in ethanol, methanol and soluble in water.

Table 3: Solubility Studies

Solvent	Solubility

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Ethanol	Freely soluble
Methanol	Freely soluble
Water	Soluble

FT-IR Spectral Studies:

FT-IR spectroscopy study was carried out separately to check the compatibility between the drug (Ramipril) polymer (EC, HPMC). The FT-IR was performed for drug, polymer and physical mixture of the drug and polymer. The spectra obtained from FT-IR spectroscopy studies are shown in figures 1 to 5 and the characteristics peaks obtained are shown in table 4 to 7.

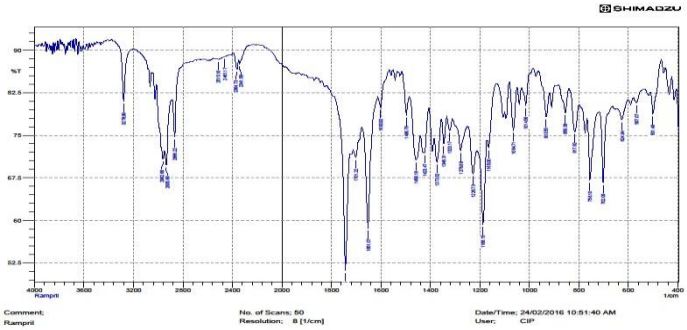

Figure 1: FTIR Spectrum of Ramipril

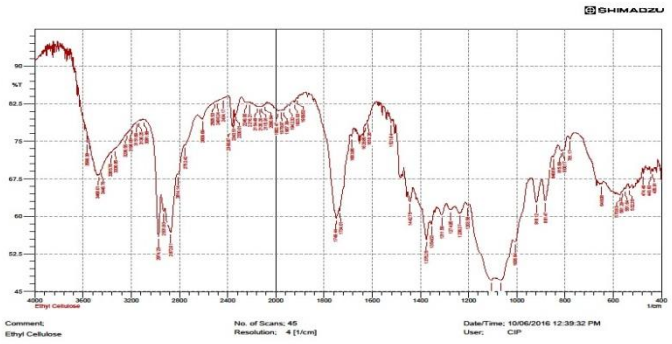

Figure 2: FTIR Spectrum of Ethyl Cellulose

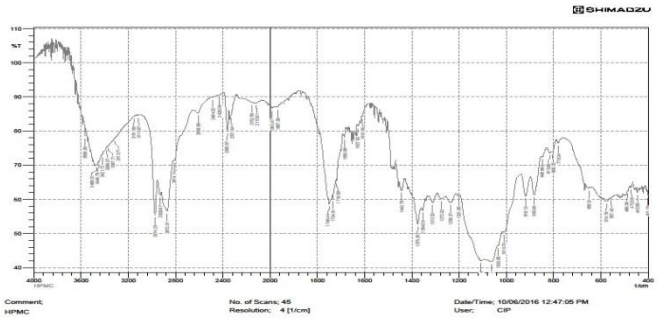

Figure 3: FTIR Spectrum of HPMC

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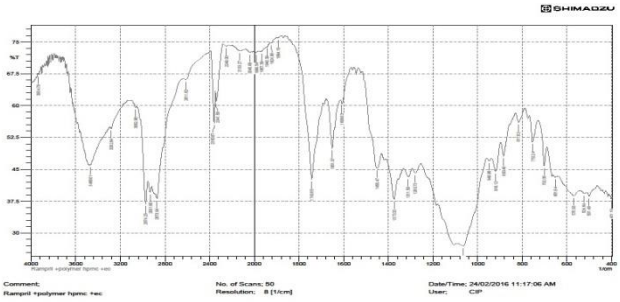

Figure 4: FTIR Spectrum of Ramipril, EC and HPMC

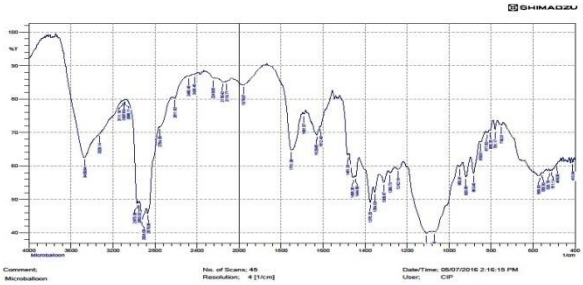

Figure 5: FTIR Spectrum of Floating Microballoons of Ramipril

Table 4. Characteristics peaks of Ramipril

S. No.	Functional Group	Absorption Peaks (cm $^{-1}$)
1.	-NH stretching	3000
2.	-OH stretching	2900
3.	-CH aromatic stretching	2800
4.	-CH aliphatic stretching	1730
5.	-C=O	1680
6.	-CH aromatic bending	1360
7.	-CH aliphatic bending	1320

Table 5. Characteristics peaks of Ethyl cellulose

S. No.	Functional Group	Absorption Peaks (cm $^{-1}$)
1.	-CH alkane stretching	3010,3040
2.	-CH aromatic stretching	2800
6.	-CH alkane bending	1360
7.	-CH aromatic bending	870

Table 6. Characteristics peaks of HPMC

S. No.	Functional Group	Absorption Peaks (cm $^{-1}$)

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1.	-OH stretching free	3560
2.	-OH stretching phenols	1200
3.	-CH alkane stretching	3010,3040
4.	-CH aromatic stretching	2800
5.	-CH alkane bending	1360
6.	-CH aromatic bending	870
7.	$-CH_3$ bending	1380

Table 7. Characteristics peaks of Microballoons

S. No.	**Functional Group**	**Absorption Peaks (cm^{-1})**
1.	-NH stretching	3000
2.	-OH stretching	2900
3.	-CH aromatic stretching	2800
4.	-CH aliphatic stretching	1730
5.	-C=O	1680
6.	-CH aromatic bending	1360
7.	-CH aliphatic bending	1320

After performing FTIR of the Ramipril with excipients, it was found that the peaks obtained in drug mixture were in between the range of main principle peaks and were found to be very near to previously performed FTIR of pure drug Ramipril. No major deviation in peaks were obtained in IR spectra, hence this indicates that drug was compatible with other ingredients. The results of IR spectra of Ramipril suggest that selection of excipient for floating microballoons were suitable. Hence it cannot alter the therapeutics efficacy of Ramipril and it also support to continue further research works.

Determination of λ max for Ramipril:
The absorption spectrum of pure drug was scanned 200-400 nm. The λ max of pure drug was to be found 225 nm.

Table 8. Wavelength at which maximum absorption of Ramipril occur

S. No.	**Solvent**	**λ max**
1.	0.1N HCL	225 nm

Calibration curve of Ramipril in 0.1N HCL:
Standard calibration curve in table 6.8 shows the absorbance of Ramipril at different concentration ranging from 2 to 10 µg/ml in 0.1N HCL. Fig. 6.5 shows the standard curve of Ramipril, which was found to be linear at 225 nm. The regression value was found to be 0.99.

Table 9. Data for calibration curve of Ramipril in 0.1N HCL at 225 nm.

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Concentration (µg/ml)	Absorbance (nm)
2	0.135
4	0.275
6	0.385
8	0.495
10	0.678

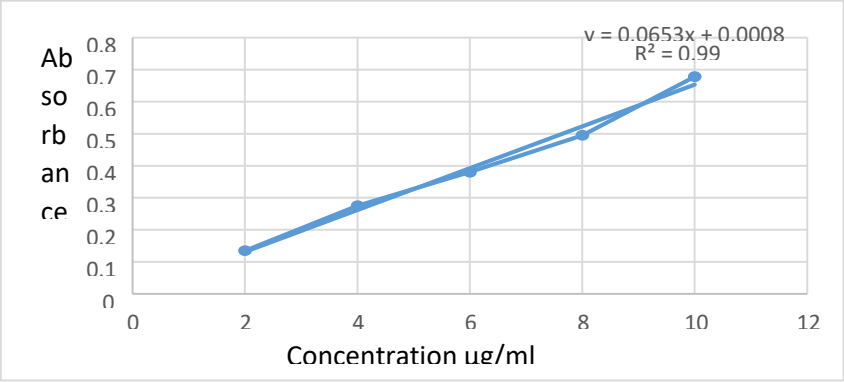

Fig. 6. Standard calibration curve of Ramipril in 0.1N HCL at 225 nm

Preparation of Floating Microballoons:

The Ramipril floating microballoons were prepared by emulsion solvent evaporation method using different proportion of polymers. Liquid paraffin solution containing tween 80 (1%) was used to obtained microballoons. The polymer HPMC and EC used to formulate the microballoons. Floating microballoons were prepared by gradually increase EC concentration with a fixed conc. of HPMC.

Evaluation of Floating microballoons

Particle Size Determination:

The microballoons were observed with microscope (100 particles) and were founed to be range size from 800 to 950 µm.

Percentage Yield: The Percentage yield of microballoons of all the formulation was found to be in the range of 70 to 86.66 %.

Table 10. Percentage yield of Ramipril

Formulation	Percentage Yield (%)
F1	73.3
F2	75
F3	70
F4	86.66
F5	71
F6	77

Determination of Drug Entrapment Efficiency:

The entrapment efficiency increased with increase in Ethyl cellulose concentration. This could be due to the higher permeability characteristics of HPMC which facilitate the diffusion of part of entrapped drug to the medium during the preparation of microballoons. The entrapment efficiency of all formulations are shown in table 7.9.

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Table 11. Drug entrapment efficiency of Ramipril floating microballoons

Formulation	Entrapment efficiency (%)
F1	52.1
F2	59.8
F3	61.1
F4	78.1
F5	69.8
F6	74.1

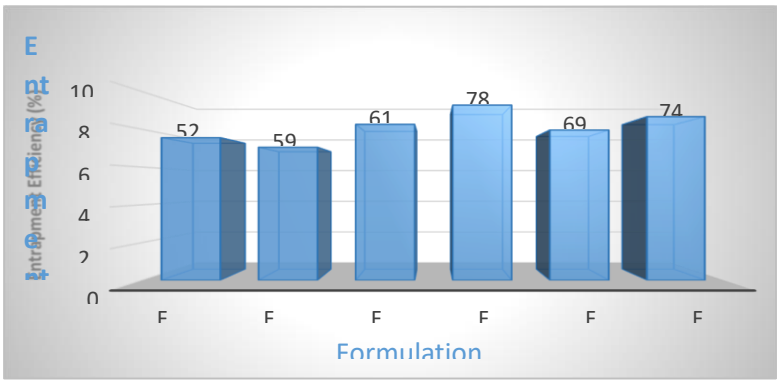

Figure 7. Drug Entrapment Efficiency of all formulations

Table 12. Percentage of Buoyancy of floating microballoons of Ramipril

Formulation	Buoyancy Percent (%)
F1	75.6
F2	70.53
F3	82.69
F4	92.85
F5	79.65
F6	86.75

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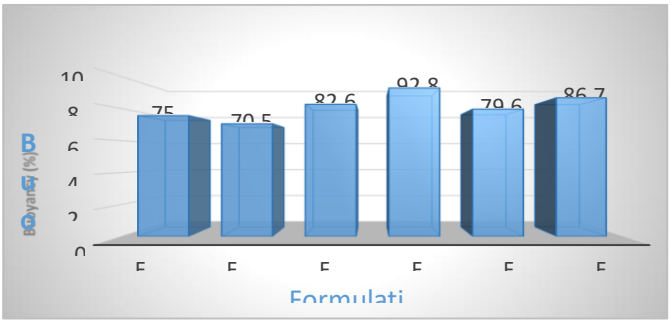

Figure 8. Buoyancy Percent of all formulations.

Swelling Index:

Swelling index observed in two different medium i.e. distilled water and 0.1 N HCL. Microballoons showed more swelling in distilled water.

Table 13. Swelling Index in distilled water at 15 hr.

Formulation	**Swelling Index**
F1	26
F2	52
F3	63
F4	72
F5	78
F6	84

Table 14. Swelling Index in 0.1 N HCL at 15 hr.

Formulation	**Swelling Index**
F1	121
F2	140
F3	110
F4	118
F5	124
F6	126

***In vitro* Drug Release Studies:**

Drug release from microballoons decreased with increase in EC concentration due to its less permeability. It increases the Polymer matrix density leading to decrease in drug release from the microballoons.

Table 15. In vitro release profile of all formulations.

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Time (hr)	F1 (%DR)	F2	F3	F4	F5	F6
1.	13.54	6.11	11.11	21.1	16.11	15.32
2.	21.73	11.21	18.33	32.29	18.33	24.11
3.	35.41	20.21	29.64	43.22	36.30	31.18
4.	44.26	26.31	34.86	50.22	50.30	42.19
5.	53.28	33.43	49.78	60.11	55.31	50.11
6.	63.59	40.58	54.28	69.22	62.29	63.25
7.	72.15	48.39	63.96	76.22	70.34	69.26
8.	83.24	57.53	75.48	85.22	74.87	74.56
9.	88.76	68.21	80.75	94.55	80.16	79.81
10.	92.54	79.52	84.32	98.22	86.17	83.17

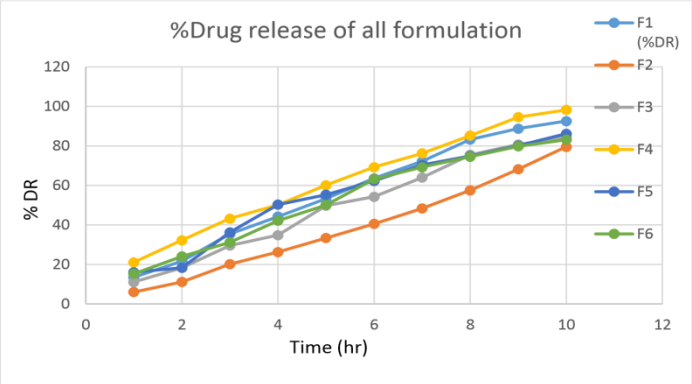

Figure 9. In vitro release profile of all formulations

Table 16. Best Fit Model for all formulations

Formulation	**Zero order (R^2)**	**First Order (R^2)**	**Higchi Model (R^2)**	**Korsmeyer-Peppas**		**Best Fit Model**
				n	**R^2**	
F1	0.990	0.983	0.907	0.888	0.899	Zero Order
F2	0.991	0.981	0.954	0.674	0.967	Zero Order
F3	0.989	0.474	0.921	0.925	0.918	Zero Order
F4	0.994	0.970	0.907	0.962	0.929	Zero Order
F5	0.957	0.976	0.836	0.803	0.859	First Order
F6	0.980	0.977	0.934	0.781	0.911	Zero Order

DISCUSSION:

Selection of drug plays chief role before starting the research work. Before finalizing the active ingredients we did literature survey what are the work has been done. From this we can came to know that what new things we can do. As per data of literature we selected Ramipril for further work. Per formulation studied has been conducted to assess its purity. Ramipril were identified by UV spectroscopy and FTIR method. No major deviation in peaks were obtained in IR spectra, hence this manifests that there was no fundamental interaction between drug and other ingredients. Moreover solubility analysis and melting point of drugs were examined for conformation of purity of active ingredients. The above mentioned outcomes indicate that the drugs are suitable to conduct further studies.

After that an attempt to make to an attempt to make to develop floating microballoons of Ramipril with polymer HPMC and HC by solvent evaporation method. Various formulation (F1, F2, F3, F4, F5, F6) were developed by using polymer combination HPMC and EC. Developed formulations were evaluated for the parameter such as Particle size determination, Entrapment efficiency, Buoyancy test, Swelling index, Percentage yield, Drug release and Kinetic studies. Particle size determination showed that all the microballoons were in micro micrometer size. Drug entrapment efficiency revealed that the F4 and F6 (78.1, 74.1 respectively) shows higher efficiency than all the formulation and buoyancy percent shows F4 and F6 (92.85, 86.75 respectively) buoyant higher than all the formulation. Moreover percentage yield was found to be 70 to 86.66 respectively. *In vitro* dissolution study revealed that the F4 released maximum drug i.e. 98.22% at 10^{th} hours. So that F4 were considered best formulation compared to other formulations.The findings of kinetic studies indicate that all the formulations of Ramipril microballoons follow the zero order kinetics (other than F5) as the co-efficient of regression (R^2) was more near to unity as compared to the regression value of zero order and first order model. Among all the formulations it was observed that R2 value of formulation F4 and F2 were more near to one compared to other formulations.

CONCLUSION:

From the experimental result it can be concluded that floating microballoons of Ramipril with the polymer EC and HPMC can be successfully developed by solvent evaporation method. F4 formulation best among that all the formulation. Its show good float ability, buoyancy properties and in vitro drug release studies. F4 formulation exhibit the zero order kinetics. Which prolong the gastric retention time in stomach and increase the bioavailability of drug.

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